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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,666	03/08/2006	Vincent Fischetti	600-1-295PCTUS	2384

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EXAMINER	
MARX, IRENE	

ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
05/12/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,666	FISCHETTI ET AL.	
	Examiner	Art Unit	
	Irene Marx	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-17,19,22 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-17, 19, and 22-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 2/27/09 is acknowledged.

Claims 15-17, 19, and 22-23 are being considered on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Insertion of the limitation "An anti pneumococcal pharmaceutical composition comprising: (a) at least two therapeutically effective synergistic bacteriophage derived lytic enzymes obtained from bacteriophage, wherein said at least two bacteriophage derived 1ytic enzymes are selected from the group consisting of an amidase and a muramidase (or lysozyme)… wherein the combination of the at least two enzymes shows more than additive killing on a logarithmic scale" does not have support in the as-filed specification. The insertion of this limitation is a new concept because it neither has literal support in the as-filed specification by way of generic disclosure, nor are there specific examples of the newly limited genus which would show possession of the concept of providing "at least any two at least two bacteriophage derived 1ytic that are an amidase and a muramidase (or lysozyme)" as an anti-pneumococcal agent having synergistic effects as now claimed. There is only one exemplified anti-pneumococcal agent consisting of the specific bacteriophage enzymes Pa1, an amidase, and Cpl-1, a muramidase. This is not sufficient support for the new genus. "An anti pneumococcal pharmaceutical composition comprising: (a) at least two therapeutically effective synergistic bacteriophage derived lytic enzymes obtained from bacteriophage, wherein said at least two bacteriophage derived 1ytic enzymes are selected from the group consisting of an amidase and a muramidase (or lysozyme)… wherein the combination of the at least two enzymes shows more than additive killing on a logarithmic scale". This is a matter of written description, not a question of what one of skill in the art would or would not have known. The material within the

four corners of the as-filed specification must lead to the generic concept. If it does not, the material is new matter. Declarations and new references cannot demonstrate possession of a concept after the fact. Thus, the insertion of "An anti pneumococcal pharmaceutical composition comprising: (a) at least two therapeutically effective synergistic bacteriophage derived lytic enzymes obtained from bacteriophage, wherein said at least two bacteriophage derived 1ytic enzymes are selected from the group consisting of an amidase and a muramidase (or lysozyme)… wherein the combination of the at least two enzymes shows more than additive killing on a logarithmic scale" is considered to be the insertion of new matter for the above reasons.

Please see *Gentry Gallery v. Berkline* 45 U.S.P.Q.2d 1498 for a discussion related to broadening the claimed invention without support in the as-filed specification. Please see *PurduePharma v. Faulding* 56 U.S.P.Q.2d 1481 for a discussion related to a failure to describe a claimed generic concept in the narrative portion of the specification, but rather basing support on limitations in examples.

It is noted that there is no clear indication as to the substrate upon which the enzymes are synergistic in the claim designated invention. In other words, the subject of the "killing" is not indicated.

Claim Rejections - 35 USC § 112

Claim 19 and 22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Insertion of the limitation "An anti-microbial composition … comprising at least two bacteriophage derived synergistic lytic enzymes obtained from bacteriophage, wherein said at least two bacteriophage derived lyric enzymes are selected from the group consisting of an amidase and a muramidase (or lysozyme), and wherein the combination of the at least two enzymes shows more than additive killing on a logarithmic scale" does not have support in the as-filed specification. The insertion of this limitation is a new concept because it neither has literal support in the as-filed specification by way of generic disclosure, nor are there specific

examples of the newly limited genus which would show possession of the concept of providing "at least any two at least two bacteriophage derived 1ytic that are an amidase and a muramidase (or lysozyme)" as an antimicrobial agent having synergistic effects as now claimed. There is only one exemplified antimicrobial agent consisting of the specific bacteriophage enzymes Pa1, an amidase, and Cpl-1, a muramidase.

This is not sufficient support for the new genus. "An antimicrobial composition comprising at least two therapeutically effective synergistic bacteriophage derived lytic enzymes obtained from bacteriophage, wherein said at least two bacteriophage derived 1ytic enzymes are selected from the group consisting of an amidase and a muramidase (or lysozyme)… wherein the combination of the at least two enzymes shows more than additive killing on a logarithmic scale". This is a matter of written description, not a question of what one of skill in the art would or would not have known. The material within the four corners of the as-filed specification must lead to the generic concept. If it does not, the material is new matter. Declarations and new references cannot demonstrate possession of a concept after the fact. Thus, the insertion of "An antimicrobial composition comprising at least two therapeutically effective synergistic bacteriophage derived lytic enzymes obtained from bacteriophage, wherein said at least two bacteriophage derived 1ytic enzymes are selected from the group consisting of an amidase and a muramidase (or lysozyme)… wherein the combination of the at least two enzymes shows more than additive killing on a logarithmic scale" is considered to be the insertion of new matter for the above reasons.

Please see *Gentry Gallery v. Berkline* 45 U.S.P.Q.2d 1498 for a discussion related to broadening the claimed invention without support in the as-filed specification. Please see *PurduePharma v. Faulding* 56 U.S.P.Q.2d 1481 for a discussion related to a failure to describe a claimed generic concept in the narrative portion of the specification, but rather basing support on limitations in examples.

In addition, there is no clear indication as to the substrate upon which the enzymes are synergistic in the claim designated invention. In other words, the subject of the "killing" is not indicated.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15-17, 19, and 22-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15 and 19 are vague, indefinite and confusing in the recitation of "at least two therapeutically effective synergistic bacteriophage derived lytic enzymes obtained from bacteriophage". The terms "bacteriophage derived" appear redundant and should be deleted.

In addition, the phrase term "synergistic" renders claims 15 and 19 confusing, vague and indefinite in this context, since there is no clear indication of the amount, identity, nature and source of the various bacteriophage derived enzymes intended to be "synergistic" and for what purpose. It is noted that an infinite number of enzymes is comprised by the invention in an unknown amount, and it is unlikely that synergism can be determined in this context.

Moreover, there is no clear indication as to the substrate upon which the enzymes are synergistic in the claim designated invention. In other words, the subject of the "killing" is not delineated with sufficient particularity.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 15 and 19 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Fischetti *et al.* (U.S. Patent No. 6,264,945) in light of Marova *et al.* (Folia Microbiol. 38 (3), 245- 252 (1993)).

The claims are directed to a composition comprising at least two therapeutically effective synergistic bacteriophage derived lytic enzymes and in particular an amidase, a muramidase, an endopeptidase, a glucosaminidase or combinations thereof.

Fischetti *et al.* teach a composition comprising at least two therapeutically effective lytic enzymes and in particular an amidase, a muramidase, an endopeptidase, a glucosaminidase or combinations thereof. See, e.g., col. 7, lines 9-25, wherein it is taught that a phage lysin is combined with lysostaphin, an amidase. It is noted that lysostaphin comprises hexosaminidase (N-acetylglucosaminidase), glycylglycine-endopeptidase and N-acetylmuramyl-L-alanine-**amidase**, as demonstrated by Marova *et al.*.(See, e.g., page 245, paragraph 2).

Therefore, reference an enzyme composition appears to be identical to the presently claimed composition, since it comprises enzymes having the same activity as claimed. There is nothing on the record to suggest that any and all enzymes from random bacteriophages differ in their properties from the enzymes disclosed by the reference. The referenced enzyme composition appears to be identical to the presently claimed composition and is considered to anticipate the claimed composition since it has the same enzymatic activities and is taught to be effective for the same purpose. Consequently, the claimed enzyme composition appears to be anticipated by the reference.

In the alternative, even if the claimed enzyme composition is not identical to the referenced enzyme composition with regard to some unidentified characteristics, the differences between that which is disclosed and that which is claimed are considered to be so slight that the referenced enzyme composition is likely to inherently possess the same characteristics of the claimed enzyme particularly in view of the similar characteristics which they have been shown to share. Thus the claimed enzyme would have been obvious to those skilled in the art within the meaning of USC 103.

Accordingly, the claimed invention as a whole was at least prima facie obvious, if not anticipated by the reference, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments have been fully considered but they are not deemed to be persuasive.

In response to the arguments that lysostaphin "is for treatment of *Staphylococcus aureus* bacteria", it is noted that this does not mean that its amidase activity is exclusive or limited to that strain. Also, that it is noted that an enzyme is obtained or derived from any phage whatsoever is not informative about specificity. Please note that claims 16-17 and 22-23 directed to a composition comprising amidase Pal and/or muramidase Cpl-1 are not included in the anticipation rejection.

In addition, there is no clear definition of the substrate upon which the enzymes are "synergistic" in the claim designated invention. In other words, the subject of the "killing" is not delineated with particularity.

Therefore the rejection is deemed proper and it is adhered to.

Claims 15-17 and 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fischetti *et al.* (I)(U.S. Patent No. 6,264,945) taken with Marova *et al.* (Folia Microbiol. 38 (3), 245- 252 (1993)), Fischetti *et al.* (II)(U.S. Patent No. 6,056,954), Sanz *et al.* (Eur. J. Biochem. 187,409-416 (1990)) and Loeffler *et al.* (Science **294:**2170-2172).

The claims are directed to a composition comprising at least two therapeutically effective synergistic bacteriophage derived lytic enzymes and in particular an amidase and a muramidase, in particular Cpt-1 and Pal.

Fischetti *et al.* (I) teach a composition comprising at least two therapeutically effective lytic enzymes and in particular an amidase and a muramidase. See, e.g., col. 7, lines 9-25, wherein it is taught that a phage lysin is combined with lysostaphin. It is noted that lysostaphin is an amidase that comprises hexosaminidase (N-acetylglucosaminidase), glycylglycine-endopeptidase and N-acetylmuramyl-L-alanine-**amidase**, as demonstrated by Marova *et al.* (See, e.g., page 245, paragraph 2).

The composition of Fischetti *et al.* differs from the claimed composition in that it is not specifically indicated as being solely "bacteriophage derived" or "obtained" and in comprising Pal and Cpl-1.

However, Fischetti *et al.* (II) strongly suggests the use of several bacteriophage lytic enzymes in combination. See, e.g., col. 13, lines 16-25.

In addition, Loeffler *et al.* teach the favorable properties of the cell wall degrading enzyme Pal, while Sanz *et al.* teach the favorable properties of Cpl-1 lysozyme. The references indicate that both enzymes are active on the dangerous pathogen *P. pneumoniae*. See, e.g., respective Abstracts and Loeffler *et al.,* page 270, paragraph 1; Sanz *et al.,* page 410, paragraph 5. Therefore, one of ordinary skill in the art would have included them at the time the claimed invention was made in an anti-pneumococcal or antimicrobial composition with a reasonable expectation of success.

One of ordinary skill in the art would have had a compelling motivation in providing a combination of various bacteriophage derived enzymes as taught by Fischetti *et al.* (II) and/or replacing the lysostaphin degradative enzymes in the composition of Fischetti *et al.* (I) with various bacteriophage derived enzymes having the same or similar degradative activity, such as Pal and Cpl-1 for their recognized beneficial properties that include specificity for certain dangerous pathogenic bacteria as well as stability.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify the composition of Fischetti *et al.* (I) by replacing the degradative enzymes therein with bacteriophage derived degradative enzymes as taught by Fischetti *et al.* (II) or adding the specific bacteriophage degradative enzymes Pal and Cpl-1 as suggested by the teachings of Loeffler *et al.* and Sanz *et al.* for the expected benefit of providing an enzyme composition that is known to have powerful degradative activity and suitable for the control of dangerous and resistant bacterial pathogens such as *P. pneumoniae.*

Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments have been fully considered but they are not deemed to be persuasive.

Applicant appears to argue that the combination of references does not teach or suggest each and every element and limitation of the claim. That lysostaphin "is for treatment of *Staphylococcus aureus* bacteria" does not mean that its amidase activity is limited to that strain.

Also, that it is not a phage enzyme does not mean that its activity is substantially different from that of any random phage amidase.

The allegations that none of the references alone, or in combination teaches or suggests the particular and specific claimed compositions and combinations of synergistic bacteriophage derived lytic enzymes, including for use as instantly claimed are noted. However, there is no clear indication as to the substrate upon which the enzymes are synergistic in the claim designated invention. In other words, the subject of the "killing" is not delineated with sufficient particularity. Moreover "synergism" has not been demonstrated for any of the compositions as claimed.

Furthermore, the intended use of the composition does not distinguish the composition since such undisclosed use is a natural effect of the compositions taught by the references. In order to be limiting, the intended use must create a structural difference between the claimed composition and the prior art composition. In the instant case, the intended use does not create a structural difference, thus, the intended use is not limiting. "The claiming of a new use . . . which is inherently present in the prior art does not necessarily make the claim patentable." *In re Best*, 195 USPQ 430, 433 (CCPA 1977). When applicant claims a "composition in terms of function . . . and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the Examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection" (MPEP 2112).

In addition, applicant fails to appreciate that the invention as claimed is not specific as to the concentrations of phage enzymes, including the concentration of the amidase Pal and the muramidase Cpl-1 required to make the composition "synergistic" as claimed. For purposes of argument only, it will be assumed that *S. pneumonia* is the subject "killed", even though this effect is not the subject of the claimed invention.

Only at Figure 2 of the as-filed specification are data provided that suggest the achievement of a combination of an amidase and a muramidase "wherein the combination of the at least two enzymes shows more than additive killing on a logarithmic scale" for certain, specific strains of *S. pneumoniae*. These data are obtained by treating samples of certain, specific strains of *S. pneumoniae* with the specific amidase Pal and muramidase Cpl-1 at specific concentrations. The record is not informative regarding the use of further unidentified phage

which are at least one muramidase and amidase enzymes in the composition to achieve the "killing" of *S. pneumoniae* or the use of specific enzymes at other concentrations. There is nothing on this record to suggest that providing at least an unidentified bacteriophage muramidase and a bacteriophage amidase or even the specific amidase Pal and muramidase Cpl-1 in undisclosed amounts will have effects "wherein the combination of the at least two enzymes shows more than additive killing on a logarithmic scale" of any microbes, including *S. pneumoniae*

Therefore the rejection is deemed proper and it is adhered to.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Irene Marx whose telephone number is (571) 272-0919. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 .

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Irene Marx/
Primary Examiner
Art Unit 1651